PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 35930PC01	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000399	International filing date *(day/month/year)* 23.12.2004	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07D401/00 C07D211/00 A61P1/00 A61P9/00 A61P13/00 A61K31/445 A61K31/404 A61K31/428 A61K31/4184 A61K31/415 A61K31/343		
Applicant BIO-MEDISINSK INNOVASJON AS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 16.11.2005	Date of completion of this report 24.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Strack, E Telephone No. +31 70 340-4760

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000399

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-69 as originally filed

   Claims, Numbers

   1-21 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17-21 (partially)

because:

☒ the said international application, or the said claims Nos. 17-21 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000399

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☒ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
   - ☐ complied with.
   - ☒ not complied with for the following reasons:

     see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:
   - ☒ all parts.
   - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	17-21 (see separate sheet)

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 17-21 relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no report has been drawn up with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I)PCT).

Re Item IV

Lack of Unity

The problem to be solved by the present application is to provide a compound for medical treatment of disorders associated with peripheral 5HT receptors.

The proposed solution is to use a compound falling under claims 1-10, in particular
(1) compounds falling under Formula VI
(2) compounds falling under Formula IV-P.

The use of compounds of claims 1-10 for the treatment of disorders associated with peripheral 5HT receptors represents the common inventive concept which may, a priori, unify the different problems mentioned above.

WO9610027 (page 1, line 24-26 and compounds no. 33 and 55), JP11292846 (see PAJ and CA abstract) and EP1149832 (paragraph 0005, example 9, test examples 1 and 2, claims 1-11) disclose compounds falling under Formula I of the present invention for the treatment of gastrointestinal motility disorders known to be associated with peripheral 5HT receptors (siehe Mutschler et al.: Arzneimittelwirkungen, WVG, Stuttgart, 2001, page 462-466).

In addition, the applicant is reminded that the use of a substance for the manufacture of a medicament for the treatment of a specific disease would still only be patentable if this use was new and inventive. Patenting a use in form of a different or newly-specified mechanism of action is impossible. In fact, the discovery of such a mechanism of action

(here: "known to be associated with peripheral 5HT receptors") does not represent an invention as the resulting technical effect remains the same (treatment of the same groups of diseases with the same compounds). In the present case, the discovery of an alternative mechanism of action ("known to be associated with peripheral 5HT receptors") would not add a new or improved technical effect to well-known medical uses; the technical effect is not modified by the discovery of an alternative mechanism of action. Therefore, the present mechanism of action cannot, as a matter of principle, serve as common single inventive concept in the sense of Rule 13.1 PCT, which would link the present inventions in the sense of Rule 13.2 PCT.

Therefore, the use of compounds of the compounds of claims 1-10 for the treatment of disorders associated with peripheral 5HT receptors is known in the prior art and cannot fulfil the role of special technical feature in the sense of Rule 13.2 PCT and can also not serve as a single general inventive concept in the sense of Rule 13.1 PCT linking the solutions (1) and (2).

Consequently, the present application lacks unity of invention, and the solutions not belonging to a common inventive concept are identified as the different subjects listed as follows:

1
claims 11 (completely); 1-10,13-21 (partially)

Use of the compounds falling under formula VI for treating a cardiovascular, gastrointestinal or lower urinary tract disorder and the compounds of formula VI per se

2
claims 12 (completely); 1-10,13-21 (partially)

Use of the compounds falling under formula IV-P for treating a cardiovascular, gastrointestinal or lower urinary tract disorder and the compounds of formula IV-P per se

Each of the inventions is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a

whole, makes over the prior art.

In the present application, no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Article 33(4) PCT

The subject-matter of claims 17-21 involves compositions or substances in a method of treatment of the human/animal body. For the assessment of these claims on the question whether they are industrially applicable, no unitary criteria exist in the PCT Contracting states. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise the subject-matter of claims related to the use of a compound in medical treatment as industrially applicable. However, the EPO may allow claims related to a known compound in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.2 Reference is made to the following documents:

D1: MÜLLER-LISSNER S A ET AL: "Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation." ALIMENTARY PHARMACOLOGY & THERAPEUTICS. OCT 2001, vol. 15, no. 10, October 2001 (2001-10), pages 1655-1666, XP008046982 ISSN: 0269-2813

D2: SANGER G J ET AL: "SB-207266: 5-HT4 receptor antagonism in human isolated gut and prevention of 5-HT-evoked sensitization of peristalsis and increased defaecation in animal models" NEUROGASTROENTEROLOGY AND MOTILITY 1998 UNITED KINGDOM, vol. 10, no. 4, 1998, pages 271-279, XP008049803 ISSN: 1350-1925

V.3 Novelty

V.3.1 Invention 1

Document D1, which is considered to represent the most relevant state of the art for the first invention, discloses the use of tegaserod for the treatment of gastrointestinal disorders mediated by the 5HT receptor.

From this, the subject-matter of **invention 1** differs in that specific novel tegaserod derivatives and analoga according to Formula VI are used.

The subject-matter of invention 1 in as far as it is restricted to the compounds of Formula VI is therefore considered novel (Article 33(2) PCT).

V.3.2 Invention 2

Document D2, which is considered to represent the most relevant state of the art for the second invention, discloses the use op the 5HT4 receptor antagonist SB-207266, for treating symptoms of Irritable Bowel Syndrome.

From this, the subject-matter of **invention 2** in that novel compounds are used in which n-butyl is replaced by the substituents L-A according to Formula IV-P.

The subject-matter of invention 2 in as far as it is restricted to the compounds of Formula IV-P is therefore considered novel (Article 33(2) PCT).

V.4 Inventive Step

V.4.1 Invention 1

With regard to D1 (see section V.3.1) the technical problem to be solved by the first invention may be regarded as to provide compounds for the treatment of disorders associated with peripheral 5HT receptors with lower side effects when compared to the compounds of D1, i.e. tegaserod.

The first invention proposes to use compounds falling under Formula VI.

No indications were found that would have led the skilled person to modify tegaserod (D1, abstract) in any specific way in order to obtain the compounds of the present invention to solve the problem posed.

However, there is reasonable doubt that the problem underlying the present application has indeed been solved:

Allegedly, after derivatisation of known compounds (e.g. compounds of D1), which would lead to compounds of invention 1, the derivative obtained has a lowered pKb value when compared to the original compound.

Again, allegedly, the decrease of the pKb value (influencing the blood-brain barrier passage) leads to a decrease of side effects mediated by CNS-located 5HT receptors.

However, the description does not demonstrate this technical effect:

- No in-vitro data is given to demonstrate changes in pKb/pKd values resulting from derivatisation of compounds structurally representative for the **whole scope** of the invention (e.g. compounds of D1).

- It is not demonstrated that side effects mediated by CNS-located 5HT receptors are indeed decreased following derivatisation and resulting decrease of the pKb value.

Therefore, it is not established that any therapeutic effect occurs due to said lowering of the pKb value.

Thus, in the present case, the absence of in-vitro or in-vivo data demonstrating the alleged

mechanism (changes in pKb/pKd) and the desired therapeutic effect (decrease of side effects) as a result of the alleged mechanism means that the problem underlying the invention cannot be considered to be solved over the whole scope of the claims.

The solution to the problem proposed in invention 1 is therefore considered not to involve an inventive step (Article 33(3) PCT).

V.4.2 Invention 2

With regard to D2 (see section V.3.2) the technical problem to be solved by the second invention may be regarded as the provision of compounds for the treatment of disorders associated with peripheral 5HT receptors with lower side effects when compared to the compounds of D2, i.e. SB-207266.

The second invention proposes to use compounds falling under Formula IV-P.

No indications were found that would have led the skilled person to modify SB-207266 (see D2) in any specific way in order to obtain the compounds of the present invention to solve the problem posed.

However, there is reasonable doubt that the problem underlying the present application has indeed been solved:

Allegedly, after derivatisation of known compounds (e.g. compound of D2), which would lead to compounds of invention 2, the derivative obtained has a lowered pKb value when compared to the original compound.

Again, allegedly, the decrease of the pKb value (influencing the blood-brain barrier passage) leads to a decrease of side effects mediated by CNS-located 5HT receptors.

However, the description does not demonstrate this technical effect:

- No in-vitro data is given to demonstrate changes in pKb/pKd values resulting from

derivatisation of compounds structurally representative for the **whole scope** of the invention (e.g. compounds of D2).

- It is not demonstrated that side effects mediated by CNS-located 5HT receptors are indeed decreased following derivatisation and resulting decrease of the pKb value.

Therefore, it is not established that any therapeutic effect occurs due to said lowering of the pKb value.

Thus, in the present case, the absence of in-vitro or in-vivo data demonstrating the alleged mechanism (changes in pKb/pKd) and the desired therapeutic effect (decrease of side effects) as a result of the alleged mechanism means that the problem underlying the invention cannot be considered to be solved over the whole scope of the claims.

The solution to the problem proposed in invention 2 is therefore considered not to involve an inventive step (Article 33(3) PCT).